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Clinical, Morphological, and Biochemical Phenotype of a New Case of Ehlers-Danlos Syndrome Type VIIC

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Ehlers-Danlos syndrome (EDS) type VIIC is a newly recognized human disorder which results from failure to remove the amino-terminal propeptide of type I procollagen. Four cases of EDS type VIIC have been reported, and here we describe a fifth case. The propositus was a 1,445 g male infant born at 30 weeks of gestation following premature rupture of membranes. He had wide fontanelles, prominent eyes with swollen eyelids and blue sclerae, anteverted nostrils, micrognathia, umbilical hernia, short stubby fingers, and cutis laxa with hirsutism. At age 3 months, during the repair of the umbilical hernia, he was noted to have unusual skin fragility. Examination of skin by scanning electron microscopy showed frayed collagen fibrils, and transmission electron microscopy showed the hieroglyphic collagen fibril morphology characteristic of the disorder. As reported in other cases, cultured fibroblasts synthesized type I procollagen that was very poorly processed at the amino-terminal propeptide cleavage site. The 5 known cases of human EDS type VIIC characterize a distinct clinical phenotype, making this condition recognizable at birth before manifestation of severe skin fragility. The diagnosis can be confirmed by biochemical studies of type I procollagen synthesis and by electron microscopic examination of skin. Am. J. Med. Genet. 68:25–28, 1997 © 1997 Wiley-Liss, Inc.

KEY WORDS: Ehlers-Danlos syndrome type VIIC; human dermatosparaxis; skin fragility; type I collagen

INTRODUCTION

Ehlers-Danlos syndrome (EDS) type VIIC is a newly recognized, presumably autosomal recessive disorder characterized by extreme skin fragility. It is analogous to dermatosparaxis, which has been described in several non-human species. The disorder results from deficient activity of type I procollagen N-proteinase, an extracellular enzyme which is responsible for removal of the amino-terminal propeptide of type I procollagen. As a consequence, there is accumulation of pN type I procollagen in the dermis [Smith et al., 1992; Nusgens et al., 1992].

Only 4 cases of EDS type VIIC have been reported [Wertelecki et al., 1992; Smith et al., 1992; Nusgens et al., 1992; Petty et al., 1993; Reardon et al., 1995]. This is a report of a fifth patient with EDS type VIIC who shows skin fragility and characteristic physical changes. The distinct clinical phenotype manifested by these 5 patients makes EDS type VIIC identifiable in the neonatal period before the severe skin fragility is noted.

CASE CLINICAL REPORT

A.A. was born at 30 weeks of gestation to a 26-year-old gravida 2 parity 1 mother and 32-year-old father. Both parents were born in the state of Jalisco, Mexico but in 2 different towns and denied consanguinity. The mother had premature rupture of membranes at 26 weeks of gestation and was hospitalized for 4 weeks. Labor was induced when severe oligohydramnios developed. The infant weighed 1,445 g (75th centile), measured 42 cm (75th centile), and had an OFC of 27.5 cm (50–75th centile). He had a wide open anterior fontanelle measuring 7 × 5 cm. The facial appearance was unusual with hirsutism of the forehead, protruding eyes with swollen eye lids, blue sclerae, cloudy corneae, and epicanthal folds, anteverted nostrils, and micrognathia (Fig. 1). The palate was intact and not high. There was a 3 cm umbilical hernia (Fig. 2). The fingers were short (Fig. 3). The skin showed cutis laxa and generalized hirsutism (Figs. 2, 3). Radiographs of the skull at birth showed large fontanelles. An echocardiogram was normal and a cranial ultrasound showed a small parenchymal hemorrhage. Ophthalmologic examination

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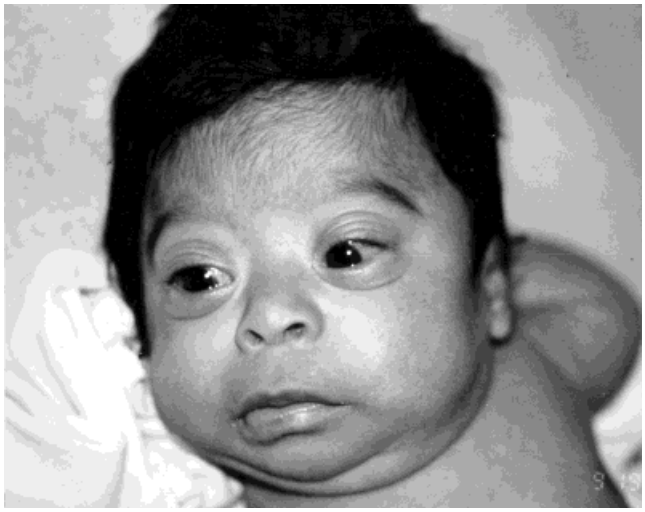

Fig. 1. Age 3 months. Note hirsutism of forehead, swollen eyelids, epicanthal folds, antiverted nostrils, and micrognathia.

Fig. 3. Hand with short stubby fingers and redundant skin.

showed cloudy corneae but no other abnormalities. Karyotype from peripheral blood was normal (46,XY).

At 3 months, the infant's umbilical hernia was repaired. During that admission unusual skin fragility and a tendency to bleed were noted. A tourniquet applied to his arm cut through the skin, exposing the bone. Profuse bleeding occurred at the site of a skin biopsy, and stapling was necessary because the skin did not hold the sutures. The wound healed rapidly without forming a scar.

At ages 5 months and 8 months, the infant was hospitalized with pneumonia. Radiographs of the chest showed severe pulmonary hyperinflation, right lobe atelectasis, increased basilar bronchial markings, and decreased volume of the left lower lobe. He also had an episode of pneumonia while in the neonatal intensive care unit. A computerized tomogram of the chest at 10 months showed patchy density in the right upper lobe and posterior segment of the right lower lobe, indicating parenchymal disease.

Between the ages 3 months and 10 months, shortening of the arms and thighs became more apparent and his height diminished progressively from the 50th centile to much below the 5th centile. No myopia was noted on two eye examinations. No joint laxity was present. Renal ultrasound examination at birth showed bilateral hydronephrosis, but a repeat ultrasound examination and voiding cystourethrogram at age 9 months showed normal findings. No osteopenia was present at 9 months. His skin was easily bruised when pressure was applied, but no excessive bleeding occurred after intramuscular injection of vaccines. He had a social smile at 3.5 months, rolled over at 8 months, and was verbalizing consonant sounds at 10 months.

Fig. 2. Age 3 months. Note umbilical hernia, short limbs with cutis laxa.

METHODS

Transmission Electron Microscopy

Skin was fixed in 2.5% glutaraldehyde, postfixed in 3% osmium tetroxide, dehydrated with ascending grade of ethanol, and embedded in poly/bed 812 (Polysciences, Warrington, Pennsylvania). Thin sections (500 Å) were cut with a diamond knife using a LKB microtome, collected on single-hole Formvar-coated grids, stained with uranyl acetate and lead citrate, and viewed with a Zeiss 902A transmission electron microscope.

Scanning Electron Microscopy

Skin was fixed in 2.5% glutaraldehyde, rinsed with phosphate buffer, dehydrated with ascending grades of ethanol, immersed in hexamethyldisilazane for 5 minutes, and air-dried. The sample was then mounted, sputter-coated with gold palladium, and viewed with a Hitachi S405 scanning electron microscope.

RESULTS

By transmission electron microscopy, collagen fibrils cut in cross-section showed the characteristic "hieroglyphic"

pattern seen in previous patients with EDS type VIIC (Fig. 4 a,b) [Wertelecki et al., 1992; Smith et al., 1992; Nusgens et al., 1992; Petty et al., 1993; Reardon et al., 1995]. Fibrils in longitudinal section appeared frayed and did not show the regular banding pattern typical of fibrils from control individuals. By scanning electron microscopy frayed fibrils, similar to those seen in other patients with EDS type VIIC, were observed (data not shown). As observed in previously reported cases, type I procollagen synthesized by cultured fibroblasts in the presence of dextran sulfate showed accumulation of pNα1 (I) chains and there was little conversion to mature type I collagen molecules (Fig. 5).

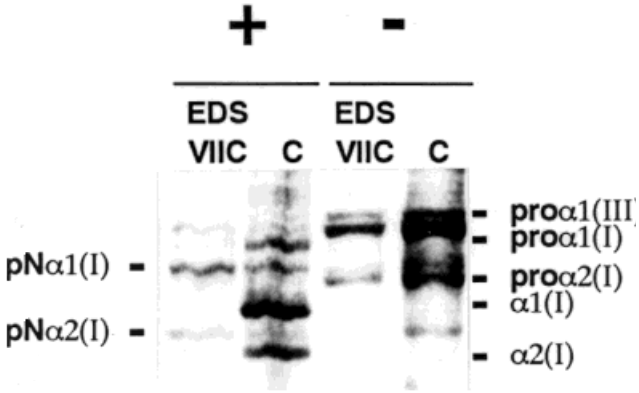

Fig. 5. Procollagen processing by cultured dermal fibroblasts from the EDS type VIIC patient (EDS VIIC) and a control (C). Cells were labeled with [3H]-proline in the presence (+) or absence (−) of dextran sulfate, and protein secreted into the medium were harvested and separated by SDS-polyacrylamide gel electrophoresis [Bonadio et al., 1985]. Note that in the presence of dextran sulfate, which enhances the conversion of procollagens to collagens [Batemen and Golub, 1990], pNα chains accumulate in the EDS VIIC sample and there is little synthesis of α chains, reflecting the reduced activity of the N-proteinase.

DISCUSSION

Dermatosparaxis, a well-described autosomal recessive disorder in various domesticated animals, is characterized by extreme skin fragility. The disorder results from failure to process type I procollagen to collagen due to reduced activity of type I procollagen N-proteinase, which cleaves the amino-terminal propeptide from type 1 procollagen. Human dermatosparaxis was recognized in 1992 in 3 patients and shown to result from a similar biochemical defect [Wertelecki et al., 1992; Smith et al., 1992; Nusgens et al., 1992; Petty et al., 1993]. The term EDS type VIIC is used to distinguish the phenotype from EDS type VIIA and VIIB, autosomal dominant conditions. In EDS type VIIA and VIIB, processing at the type I procollagen amino-terminal propeptidase cleavage site is reduced due to mutations that abolish the processing site in either the α1(I) or α2(I) chain of type I procollagen, respectively.

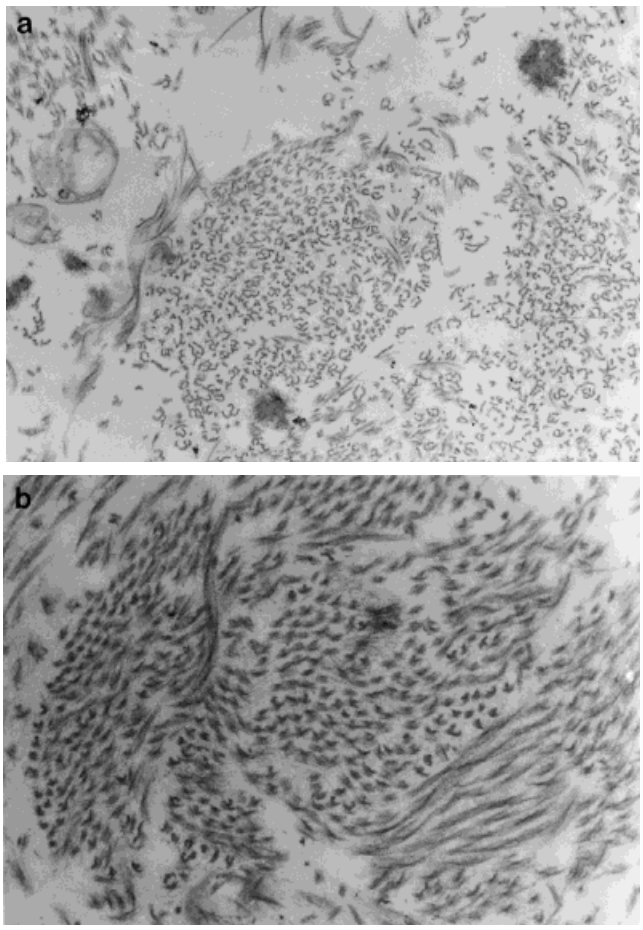

Fig. 4. **a, b**: Transmission electron micrographs of skin showing the characteristic "hieroglyphic" collagen fibrils. Original magnification: a, × 14,800; b, × 24,500.

The phenotypes of the 5 described EDS type VIIC patients, including the present case, are strikingly similar to each other, and permit identification of affected individuals neonatally. The most consistent anomalies in EDS type VIIC are premature birth due to premature rupture of membranes, large fontanelles, edema of eyelids, blue sclerae, micrognathia, umbilical hernia, short fingers, cutis laxa and extreme skin fragility, easy bruisability, and postnatal short stature (Table I). Myopia and joint laxity may manifest later in childhood. The child in this report had recurrent pneumonia with radiographic pulmonary parenchymal changes. Occasional findings of pulmonary bullae, pneumothorax, and weakness of the supporting bronchial walls leading to bronchiectasis are pleuropulmonary abnormalities of EDS type I. Two previous patients with EDS type VIIC had pneumothorax (Table I) and this disorder also appears to have a risk of pulmonary complications.

In all 5 patients, the diagnosis of EDS type VIIC was made after skin fragility was demonstrated. However, only one patient had skin tears at birth [Petty et al., 1993] and in others skin fragility was recognized between 3 months and age one year. The consistent and unique nature of the clinical defects at birth suggest that it should be possible to recognize the phenotype prior to demonstrated skin fragility. The wounds in younger patients healed rapidly with very little scar formation, while extensive scarring was seen in

TABLE I. Clinical Summary of Ehlers-Danlos Type VIIC

	Wertelecki et al. [1992] Smith et al. [1992] (case 1)	Smith et al. [1992] (case 2) Petty et al. [1993]	Nusgens et al. [1992]	Reardon et al. [1995]	Present case	
Sex	F	M	F	F	M	
Age (years)	2	2	2	15	1/2	
Gestation	28	35	29.5	32	30	
Premature rupture of membranes	+	+	+	+	+	5/5
Birth wt (g)	1,077 (50%)	2,345 (25–50%)	810 (5%)	2,200 (75%)	1,455 (75%)	
Length (cm)	37	45 (25–50%)	35 (10%)		42 (75%)	
OFC (cm)	26	31 (25–50%)			27.5 (25–50%)	
Large fontanelle	+	+	+	+	+	5/5
Edema of eyelids	+	+	+	+	+	5/5
Blue sclera	+	+	+	+	+	5/5
Myopia	+	?	?	+	−	2/3
Micrognathia	+	+	+	+	+	5/5
Umbilical hernia	+	+	+	+	+	5/5
Short limbs & fingers	+	+	+	+	+	5/5
Joint laxity	+	+	?	+	−	3/4
Cutis laxa	+	+	+	+	+	5/5
Skin tear at birth	−	+	−	−	−	1/5
Postnatal skin fragility	+ (7 mos)	+ (birth)	+ (1 year)	+ (9 mos)	+ (3 mos)	5/5
Easy bruisability	+	+	+	+	+	5/5
Short stature	+	+	?	+	+	4/4
Osteopenia	−	+	+	?	−	2/4
Wormian bones	?	+	+	?	− (at birth)	2/3
Other disease or anomalies	Hypothyroidism, pneumothorax	Dental laminal cyst, bicuspid aortic valves, pneumothorax			Hydronephrosis at birth, recurrent pneumonia	

the older patient who was 15 years old when the diagnosis was made [Reardon et al., 1995]. Such scarring may have resulted from repeated skin tearing or complications of skin healing such as bleeding or infection, and may have been prevented by better skin care.

In conclusion, EDS type VIIC is a distinctive disorder which is recognizable at birth by its characteristic manifestations and history of premature rupture of the membranes. Electron microscopic examination of skin or biochemical collagen analysis of type I procollagen synthesis and conversion provides a definitive diagnosis. Diagnosis before manifestation of skin fragility may help to reduce complications from trauma or surgical procedures.

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REFERENCES

Batemen JF, Golub SB (1990): Assessment of procollagen processing defects by fibroblasts cultured in the presence of dextran sulfate. Biochem J 267:573–577.

Bonadio J, Holbrook KA, Gelinas RE, Jacob J, Byers PH (1985): Altered triple helical structure of type 1 procollagen is associated with prolonged survival in lethal perinatal osteogenesis imperfecta. J Biol Chem 260:1734–1742.

Nusgens BV, Verellen-Dumoulin C, Hermanns-Le T, De Paepe A, Nuytinck L, Pierard GE, Lapiere CM (1992): Evidence for a relationship between Ehlers-Danlos type VIIC in human and bovine dermatosparaxis. Nat Genet 1:214–217.

Petty EM, Seashore MR, Braverman IM, Spiesel SZ, Smith LT, Milstone LM (1993): Dermatosparaxis in children. Arch Dermatol 129:1310–1315.

Reardon W, Winter RM, Smith LT, Lake BD, Rossiter M, Baraitser M (1995): The natural history of human dermatosparaxis (Ehlers-Danlos syndrome type VIIC). Clin Dysmorphol 4:1–11.

Smith LT, Wertelecki W, Milstone LM, Petty EM, Seashore MR, Braverman IM, Jenkins TG, Byers PH (1992): Human dermatosparaxis: A form of Ehlers-Danlos syndrome that results from failure to remove the amino-terminal propeptide of type I procollagen. Am J Hum Genet 51:235–244.

Wertelecki W, Smith LT, Byers P (1992): Initial observations of human dermatosparaxis: Ehlers-Danlos syndrome type VIIC. J Pediatr 121:558–564.